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The Neuropsychiatric Translational Revolution Still Very Early and Still Very Challenging

Lara Braff, PhD and

Department of Anthropology, School of Medicine, University of California, San Diego, La Jolla.

David L. Braff, MD

Department of Psychiatry, University of California, San Diego, La Jolla, and VISN 22, Mental Illness Research, Education, and Clinical Center (MIRECC), VA San Diego Healthcare System, San Diego, California.

Advances in knowledge of mammalian neurobiology and genomics far outpace their application to common but complex human disorders, especially those impacting brain function. Recently, Karayiorgou et al¹ argued for the almost exclusive use and funding of neuropsychiatric research using highly penetrant de novo mutations and selected animal models to illuminate the neural circuit and genomic network basis of neuropsychiatric disorders and to get Big Pharma back into central nervous system drug development. While their viewpoint reflects the great speed with which knowledge about mammalian genomics and neurobiology is proceeding, the translation of this kind of new basic science data to the bedside is proceeding at a much slower pace, making such prescriptive scientific pathways premature.² Many therapeutic advances in medicine are concentrated in accessible tissue disorders, such as coagulopathies and oncology, where diseased tissue can be directly examined and manipulated. But we largely lack such direct approaches for the relatively inaccessible brain with its complex neural circuit imbalances compared with the more discrete mitotic dysfunctions seen in oncology. Furthermore, with an increasing basic science and genomic focus in psychiatric neuroscience, we often overlook treatment advances in the area of cognitive, psychosocial, and health services interventions, either alone or in conjunction with pharmacotherapies.³ To suggest that one translational approach to complex neuropsychiatric disorders be given almost absolute scientific and funding primacy¹ is very premature indeed.

The gap between basic and applied research is not specific to neuropsychiatry. Indeed, several years ago, Nobel Laureates Goldstein and Brown⁴ pointed out that “elite” basic science journals present research that is often disarticulated from the practical clinical realities in medicine. They explained why they published more than 30 articles in the *Journal of Clinical Investigation*:

Corresponding Author: David L. Braff, MD, University of California, San Diego, Department of Psychiatry (MC 0804), 9500 Gilman Dr, La Jolla, CA 92093-0804 (dbraff@ucsd.edu)..

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Because the importance of [these] papers went beyond basic science. Editors and readers of elite basic science journals such as *Nature*, *Cell*, and *Science* would have difficulty comprehending the importance of studying fat accumulation in smooth muscle cells and hepatocytes... By publishing in the *JCI*, we were able to reach a broad audience of medically oriented scientists.⁴

In fact, both the etiological and therapeutic implications of much published basic neurobiological research remains unclear. For example, the precise genomic etiology of common (1% prevalence) yet complex neuropsychiatric disorders continues to elude us.

Based on a qualitative questionnaire administered at the 2011 Program and Executive Committees of the American College of Neuropsychopharmacology and Society of Biological Psychiatry, we found that the gap between basic science research and effective treatment—that is, between the bench and bedside—is of growing concern to senior neuropsychiatric thought leaders. Specifically, about 80% of the 60 thought leaders surveyed believe it is either important or essential for them, their colleagues, and students to see more than 30 patients who have the disorder that they are studying. Yet, nearly two-thirds of thought leaders believe that the research in high-impact basic science journals does not reflect this requisite level of knowledge of the actual neuropsychiatric disorders that are being modeled.⁵ We face some distinct research challenges in neuropsychiatry. A tissue slice of kidney or lungs or liver gives up its functional role quite easy (eg, in the lung, blood and bronchial structures are designed for gas exchange). In contrast, the brain is less accessible and is morphologically and genomically enigmatic and complex. Thus, we respectfully suggest a number of considerations for the field to create a more relevant translational research environment that narrows the gap between the bench and bedside, while broadening research foci.

Realistic Timeframes

It is important to present a realistic bench-to-bedside timetable for clinical applications of basic science findings. As noted by Collins⁶:

Despite dramatic advances in the molecular pathogenesis of disease, translation of basic biomedical research into safe and effective clinical applications remains a slow, expensive, and failure-prone endeavor. It is estimated that a new drug takes 13 years and about \$1,000,000,000 to bring to market after it has been identified.

The public should be educated that while our knowledge of basic neuroscience is advancing rapidly, translating the findings of basic research to the clinic for disease risk testing or personalized therapeutics will proceed much more slowly. For example, genetic testing for neuropsychiatric disease risk has proven to be profoundly illusory.⁷ Moreover, identification (30 years ago) of the simple autosomal dominant Mendelizing gene mutation causing Huntington disease has yet to lead to any effective treatments. Of the almost 5000 disorders with known (Mendelizing) genomic cause, only about 250 (5%) have corresponding genomically informed treatments.⁸ Which therapeutic interventions will new findings, such as dark matter gene desert regulation of DNA, lead to and when? We simply do not know.⁸ A toning down of overstated claims will help us avoid the type of public disappointment that

occurs when unrealistic therapeutic claims are made from interesting basic science findings in a range of fields from psychiatry to oncology.^{2,9,10}

Optimal Levels of Analysis

In neuropsychiatric genomics, where is the most etiological and treatment relevant information to be found? At the single nucleotide polymorphism, gene, methylome, connectome or some other “ome” level? When we have sequencing, methylation, and interactome data on patients, will we find that 70 million different genomic profiles exist for the estimated world population of 70 million schizophrenic patients? If so, what is the proper way to analyze and understand this huge amount of complex and interacting data? We do not yet know the optimal analytic pathways for these evolving extensive new data sets. Perhaps multiple hits in final common pathways may help us better understand the interactions and treatable outputs of complex genomic and neural systems.

Psychosocial Interventions

Rather than focus only on biological, molecular-based treatments (eg, see article by Karayiorgou et al¹), we must also consider how behavioral interventions can alleviate suffering and even therapeutically rearrange the brain—although we do not fully understand the exact mechanisms of such change.³ Combined neurobiological and psychosocial/cognitive interventions may offer effective therapeutics,¹¹ even as we may remain frustratingly uninformed regarding the neural and genomic substrates of any resulting therapeutic improvements.² Plus, health services approaches offer ways to optimize current efficacious but sometimes ineffective treatments.

Collaborative Relationships

We must forge more productive relationships between clinical and basic researchers and experts in related fields (eg, clinical psychology) and even seemingly unrelated fields (eg, anthropology). Such relationships ought not to focus solely on bench work (eg, informatics, de novo mutations, or genomic sequencing) over clinical or behavioral approaches, lest we reproduce the very gap between basic and applied work that troubles Goldstein, Brown, and many neuropsychiatric thought leaders. The neuropsychiatric translational revolution is still in a very early stage,^{2,12} with basic advances occurring too rapidly for their clinical implications to be quickly tested, no less reified. Currently available commercial genomic testing for disease risk is notoriously unreliable with one person’s DNA, leading to very diverse disease risk profiles from 3 different platforms.¹³

Discussion

Still, 3 possibilities (among many) may be considered here for how our translational science will advance: (1) We may continue to spend years, even decades, advancing our translational bench-to-bedside research incrementally, and our students and their students will slowly advance neurobiological and psychosocial therapies across a multiplatform and multigenerational time course. (2) Perhaps a series of serendipitous discoveries will be the basis for efficacious psychotropic drug therapies that will save the day.¹⁴ (3) Alternatively,

perhaps someone will construct a high-impact paradigm-shifting methodology. As Kuhn¹⁵ pointed out, scientific revolutions have often proceeded via radical (not gradual) shifts in paradigms.

This is not to say that the field currently lacks innovation. For example, take the National Center for Advancing Translational Sciences and related National Institutes of Health projects where all 5800 Food and Drug Administration–approved drugs are used to agnostically screen for (atheoretical) repurposing therapeutic effects.⁷ Or perhaps inducible pluripotent stem cells grown to resemble hippocampal cells or even neural circuits can be examined for possible circuit connectivity enhancements by one or another of these 5800 compounds or other molecules or environmental conditions. Hence, despite some slower than anticipated progress, there are novel therapies being developed in numerous areas, such as rapid-acting antidepressants with ketamine as a lead compound, so-called “procognitive medications,” and psychological interventions such as neuroplasticity-based sensory training for schizophrenia.^{1,11} While we await new strong inference-derived medication and psychosocial treatments, a recent article (one of many examples of important incremental research per path¹) illustrates how translational research may progress in the interim.¹⁶ In schizophrenia, low blood folate levels are associated with negative symptoms. Only patients homozygous for the 484 FOLHi (rs 20676) allele demonstrated reduced negative symptoms with active vitamin B12 and folate treatment. This strategy, merging existing molecules such as folate and vitamin B12 with common FOLHi genotype (not necessarily highly penetrant mutations), is supportive of the *N*-methyl-D-aspartate/glutamate hypofunction model of schizophrenia. This is but one tile in a complex mosaic of findings that may enable us to make progress in translational research while we await more farreachingpersonalizedtranslationaltherapeuticbreakthroughs. Thus, we have reason to be optimistic for the long-term future of neuropsychiatric translational research.

As historian Brinton¹⁷ pointed out, revolutions often pass through phases of unrealistic Jacobean optimism followed by more careful Thermadorian reflection. This seems to apply to the neuropsychiatric research revolution. Now is the time to avoid a sense of urgency,¹ while we patiently diversify our portfolio of research approaches and see how they interact with each other and what implications they hold. The challenges in this (still) early stage of the neuropsychiatric revolution^{2,6} are great, but our emerging and diverse armamentarium of solutions—both biological and behavioral—is also impressive and will likely (eventually) bear therapeutically useful fruit for the patients and families waiting at the end of the bench-to-bedside continuum.

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